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Identification of Factors Predicting Glycemic Control in New Patients with Type 2 Diabetes

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We investigated the background characteristics of new type 2 diabetic patients and identified factors predicting good glycemic control after 6 months. We selected 788 new patients who presented to the Diabetes Center of Tokyo Women's Medical University Hospital between July 2003 and March 2005 with an $HbA_{1c} \geq 6.5\%$. Based on the HbA_{1c} value after 6 months, the patients were divided into "good" and "poor" glycemic control groups ($<6.5\%$ and $\geq 6.5\%$, respectively). We compared background clinical characteristics between the 2 groups by logistic regression analysis. As a result, significant predictors of good glycemic control were no diabetic medications at baseline (odds ratio (OR)=0.46, 95%CI 0.32-0.67), a higher uric acid level (OR=1.25, 95%CI 1.09-1.42), a lower total cholesterol level (OR=0.80, 95%CI 0.68-0.93), a higher creatinine level (OR=1.07, 95%CI 1.02-1.13), a younger age (OR=0.99, 95%CI 0.97-1.00), and a shorter duration of diabetes (OR=0.98, 95%CI 0.95-1.00). Our findings may assist in the early identification of patients who are less likely to achieve good glycemic control and require intensive management to prevent diabetic complications.

Key words: type 2 diabetes, new patients, HbA_{1c}, glycemic control, electronic medical record system

Introduction

Early and persistent intensification of antidiabetic therapy is most likely to achieve optimal glycemic control and prevent complications in patients with diabetes[1]. The Kumamoto Study showed that the threshold to prevent both the onset and progression of diabetic microvascular complications in patients with type 2 diabetes is a hemoglobin A_{1c} (HbA_{1c}) level below 6.5%[2], and The Japan Diabetes Society defines "good" glycemic control as $HbA_{1c} < 6.5\%$[3]. However, only 15% of patients with type 2 diabetes taking oral hypoglycemic agents have achieved this target at our hospital, and the percentage of patients with an $HbA_{1c} < 7.0\%$ was reported to be 35.8% in the USA[4]. There have been several reports about the factors responsible for good glycemic control[5)~8)], but the factors identified were not consistent among these studies.

More than 2,500 new diabetic patients present to the Diabetes Center of Tokyo Women's Medical University Hospital every year, and the most common reason for their referral is to achieve better glycemic control. In this study, we investigated the background characteristics of new type 2 diabetic patients and identified factors predicting good glycemic control after 6 months.

Materials and Methods

The subjects were patients with type 2 diabetes who newly visited the Diabetes Center of Tokyo Women's Medical University Hospital from July 2003 to March 2005. They were directly visited our hospital or were referred by general practitioners (GPs). The inclusion criteria were an initial HbA_{1c} value above 6.5% and follow-up for at least 6 months. A total of 788 patients (501 men and 287 women) met these criteria were enrolled. Background clinical characteristics, such as the present illness, past medical history, family history of diabetes, laboratory data and baseline treatment of diabetes, were obtained from the hospital electronic medical record system. We defined that a patient had a history of alcohol consumption or smoking if

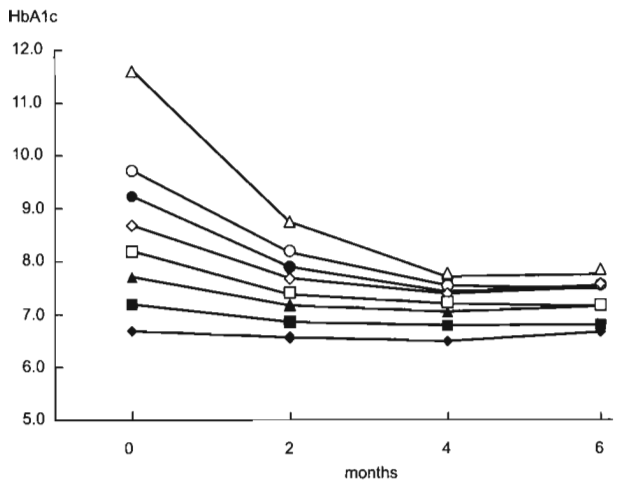

Fig. 1 HbA_{1c} profiles during 6 months of follow-up stratified by the baseline HbA_{1c} level.
◆: 6.5-7.0% (n = 93), ■: 7.0-7.5% (n = 101), ▲: 7.5-8.0% (n = 108), □: 8.0-8.5% (n = 65), ◇: 8.5-9.0% (n = 74), ●: 9.0-9.5% (n = 73), ○: 9.5-10.0% (n = 55), △: ≥ 10.0% (n = 219).

the patient had a habit even for a short period. Diabetic neuropathy and retinopathy were excluded, because these factors were difficult to evaluate at first visit.

Patients were treated by diabetologists according to the hospital protocol. Generally, at the first visit, a physician decided initial treatment policy after the examination of the patient and ordered co-medical staffs (nurse, pharmacist, and dietitian) to educate the patient. A meal tolerance test (MTT) was performed at the second visit, that was an average of 13.5 days after the first visit. Plasma glucose (PG) and serum immunoreactive insulin (IRI) were measured while fasting, as well as 60 and 120 minutes after eating a 408 kcal test meal. Homeostasis model assessment for insulin resistance (HOMA-IR) and β-cell function (HOMA-β), as well as the acute insulin response, were calculated as following: fasting serum immunoreactive insulin (FIRI) (μU/ml) ×fasting plasma glucose (FPG) (mmol/*l*)/22.5, FIRI×20/(FPG-3.5), and (immunoreactive insulin at 60 minutes after the meal (IRI_{60min})-FIRI)/(plasma glucose at 60 minutes after the meal ($PG_{60\,min}$)-FPG), respectively. We did not assess these values in patients on insulin therapy, because IRI would not reflect endogenous insulin secretion.

HbA_{1c} was measured at every visit, with an average interval of 1.6 months. Medications were changed if the target for glycemic control was not achieved after 1 to 2 months of therapy. Subjects were divided into good (<6.5%) and poor (≥6.5%) control groups according to the HbA_{1c} level after 6 months.

We compared background clinical characteristics between the 2 groups by univariate analysis; i.e. numerical and categorical data were analyzed using Student's t-test and qui-square tests, respectively. All variables that were significant ($p<0.05$) according to univariate analysis were also tested by stepwise multivariate logistic regression analysis. Furthermore, the significant predictors obtained by multivariate analysis were categorized, and odds ratios for good glycemic control were calculated. All analyses were performed with SPSS 12.0J statistical software (SPSS Inc., Chicago, USA).

Results

During 6 months of follow-up, the mean ± SD HbA_{1c} level improved from 9.0 ± 1.9% to 7.3 ± 1.4%. A series of HbA_{1c} profiles stratified by the baseline value are shown in Fig. 1. A higher baseline HbA_{1c} level was associated with a greater decrease after 6 months.

We compared background clinical characteristics between the good and poor control groups by univariate analysis. As shown in Table 1, patients with good glycemic control had a significantly higher male/female ratio, younger age, shorter duration of diabetes, no baseline medications, higher body mass index (BMI) at baseline and at 20 years old, greater maximum BMI, lower total cholesterol, lower HDL-cholesterol, higher creatinine, and higher uric acid than those with poor control. These significant variables were subsequently tested by multivariate logistic regression analysis. As shown in Table 2, the significant predictors of good glycemic control thus identified were no baseline medications, higher uric acid, lower total cholesterol, higher creatinine, younger age, and shorter duration of diabetes.

The significant predictors obtained by multivariate analysis were categorized and odds ratios for good glycemic control were calculated (Table 3). Patients treated with oral hypoglycemic agents (OHA)

Table 1 Comparison of background clinical characteristics between the good and poor glycemic control groups

	Good (218)	Poor (570)	p value
Sex (male/female)	151/67	350/220	0.040 *
Age (years)	54.6 ± 13.9	57.8 ± 12.2	0.001
Reference by GP (yes / no)	136/82	372/198	0.450
Duration of diabetes (years)	6.1 ± 8.3	8.4 ± 8.7	0.001
History of alcohol consumption (%)	56.5	52.3	0.293 *
History of smoking (%)	61.8	54.0	0.052 *
Family history of diabetes (%)	65.6	58.2	0.108 *
Baseline antihypertensive therapy (%)	33.3	34.0	0.863 *
Baseline lipid-lowering therapy (%)	20.4	27.2	0.054 *
Past history of CVD or IHD (%)	14.2	16.0	0.545 *
Baseline diabetes medication (OHA or insulin) (%)	32.6	50.5	< 0.001 *
Baseline BMI (kg/m^2)	25.1 ± 4.6	24.4 ± 3.9	0.025
BMI at 20 years old (kg/m^2)	23.3 ± 4.5	22.4 ± 3.5	0.002
Maximal BMI (kg/m^2)	28.2 ± 4.9	27.5 ± 4.2	0.036
Systolic blood pressure (mmHg)	142.5 ± 23.5	143.1 ± 23.8	0.742
Diastolic blood pressure (mmHg)	81.9 ± 12.4	81.6 ± 12.5	0.752
HbA_{1c} (%)	8.9 ± 2.1	9.1 ± 1.9	0.164
Total cholesterol (mmol/*l*)	5.28 ± 1.17	5.48 ± 1.15	0.026
HDL-cholesterol (mmol/*l*)	1.26 ± 0.35	1.36 ± 0.38	0.002
AST (U/*l*)	28.8 ± 22.4	27.1 ± 20.8	0.303
ALT (U/*l*)	36.4 ± 27.9	34.7 ± 38.2	0.533
γ-GTP (U/*l*)	66.1 ± 80.8	62.9 ± 81.2	0.623
Creatinine (μmol/*l*)	80.2 ± 69.8	67.8 ± 39.3	0.002
Uric acid (mg/dl)	5.4 ± 1.5	4.9 ± 1.3	< 0.001
Hemoglobin (g/dl)	14.2 ± 1.7	14.2 ± 1.5	0.671
Urinary protein positive (%)	31.0	26.2	0.181 *

Data are shown as the mean ± SD or %. Good and poor control groups were compared by Student's t-test or the chi-square test (asterisks).
GP: general practitioner, CVD: cerebro-vascular disease, IHD: ischemic heart disease, OHA: oral hypoglycemic agents, BMI: body mass index, HbA_{1c}: hemoglobin A_{1c}, HDL-cholesterol: High-density lipoprotein cholesterol, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: γ-glutamyl transpeptidase.

Table 2 Predictors of good glycemic control according to multivariate logistic regression analysis

	Odds ratio	95% CI	p value
Baseline OHA/insulin vs. no medication	0.46	0.32-0.67	< 0.001
Uric acid (increment of 1 mg/dl)	1.25	1.09-1.42	0.001
Total cholesterol (increment of 1 mmol/*l*)	0.80	0.68-0.93	0.005
Creatinine (increment of 10 μmol/*l*)	1.07	1.02-1.13	0.007
Age (increment of 1 year)	0.99	0.97-1.00	0.033
Duration of diabetes (increment of 1 year)	0.98	0.95-1.00	0.037

CI: confidence interval, OHA: oral hypoglycemic agents.

or insulin at baseline were less likely to achieve good glycemic control than those on diet therapy (OR: 0.49 and 0.42). Patients with higher uric acid and higher creatinine levels were more likely to achieve good glycemic control. On the other hand, patients with a higher total cholesterol level and older age were less likely to achieve good control. In addition, patients with a longer duration of diabetes (1-5 years and ≥5 years) found it harder to achieve good glycemic control than those with a short duration (<1 year) (OR: 0.32 and 0.28, respectively).

The results of the meal tolerance test (MTT) are shown in Table 4. The good glycemic control group had a larger acute insulin response compared with

Table 3 Odds ratios for the factors predicting good glycemic control

Category	n	Good (%)	Odds ratio	95% CI	p value
Baseline diabetes therapy					
No	429	34.3	1.00		
OHA	270	20.4	0.49	0.34-0.70	< 0.001
Insulin	89	18.0	0.42	0.24-0.75	0.003
Uric acid (mg/dl)					
< 4	172	19.2	1.00		
4-5	202	23.8	1.31	0.80-2.16	0.285
5-6	214	28.5	1.68	1.04-2.72	0.035
6-7	123	35.0	2.26	1.33-3.85	0.003
≥ 7	64	45.3	3.49	1.88-6.50	< 0.001
Total cholesterol (mg/dl) [mmol/l]					
< 180 [< 4.65]	187	33.2	1.00		
180-220 [4.65-5.69]	294	28.2	0.79	0.53-1.18	0.252
≥ 220 [≥ 5.69]	295	23.4	0.62	0.41-0.92	0.019
Creatinine (μmol/l)					
< 50	150	22.0	1.00		
50-70	349	24.9	1.18	0.75-1.86	0.483
≥ 70	280	34.3	1.85	1.17-2.93	0.009
Age (years)					
< 40	84	39.3	1.00		
40-50	124	33.1	0.76	0.43-1.36	0.358
50-60	242	26.0	0.54	0.32-0.92	0.023
≥ 60	338	24.0	0.49	0.29-0.81	0.005
Duration of diabetes (years)					
< 1	174	48.9	1.00		
1-5	184	23.4	0.32	0.20-0.50	< 0.001
≥ 5	430	20.9	0.28	0.19-0.40	< 0.001

CI: confidence interval, OHA: oral hypoglycemic agents.

Table 4 Comparison of meal tolerance test results between the good and poor glycemic control groups

	min	Good (125)	Poor (344)	p value
Plasma glucose (mmol/l)	0	7.7 ± 2.0	9.5 ± 2.6	< 0.001
	60	12.6 ± 2.9	14.8 ± 3.2	< 0.001
	120	11.8 ± 3.8	14.8 ± 3.8	< 0.001
IRI (μU/ml)	0	8.4 ± 6.4	9.1 ± 16.9	0.653
	60	35.8 ± 27.5	27.3 ± 24.9	0.002
	120	40.2 ± 39.6	35.0 ± 43.0	0.240
HOMA-IR		2.8 ± 2.2	3.7 ± 4.3	0.058
HOMA-β		55.2 ± 99.7	47.0 ± 221.6	0.608
Acute insulin response		6.6 ± 6.3	3.8 ± 3.6	< 0.001

Data are shown as the mean ± SD. Good and poor control groups were compared by Student's t-test.
IRI: immunoreactive insulin, HOMA-IR: homeostasis model assessment for insulin resistance, (fasting IRI) × (fasting plasma glucose)/22.5, HOMA-β: homeostasis model assessment for β-cell function, (fasting IRI) × 20/(fasting plasma glucose − 3.5), Acute insulin response: (IRI at 60 minutes − fasting IRI)/(plasma glucose at 60 minutes − fasting plasma glucose).

the poor glycemic control group, whereas HOMA-IR and HOMA-β were similar for the 2 groups.

Discussion

The HbA_{1c} level of new diabetic patients usually decreases gradually until 4 months and reaches a plateau by 6 months, as shown in Fig. 1. Therefore, we focused on the HbA_{1c} at 6 months in this study, which reflects the risk of progression of diabetic complications. We demonstrated that the baseline predictors of good glycemic control were no diabetic medications, high uric acid, low total cholesterol, high creatinine, young age, and short duration of diabetes.

Some other studies have attempted to predict glycemic control from background clinical characteristics[5)~8)]. A long duration of diabetes and prior medication are common factors related to poor glycemic control among these studies.

The reason why a longer duration of diabetes is associated with poor control[5)~8)] might be the decrease of insulin secretion over time in many patients with type 2 diabetes[6)9)]. With an increasing duration of diabetes, the decrease of postprandial

insulin secretion becomes more prominent, and postprandial β-cell responsiveness may be a more important determinant for glycemic control than overall β-cell responsiveness[10]. Our finding that the acute insulin response, but not HOMA-β, is related to glycemic control is compatible with this assumption (Table 4).

Several studies have shown that patients receiving insulin or OHA had significantly higher HbA_{1c} levels compared with patients on diet alone[7)11)~13)]. Thus, initial medication may be more effective than additional medication. Generally, the type of medication is associated with the duration of diabetes, and our patients treated by diet alone had a shorter duration of diabetes than those receiving OHA or insulin (5.9 ± 8.0 vs. 10.0 ± 8.8 years).

Our study showed that a younger age was also associated with good glycemic control. However, the results of other studies have differed[5)~7)], and rapid changes of lifestyle in each generation, access to medication, barriers to glucose testing, regular physical activity, healthy low-fat eating, or compliance with medication have been mentioned as causes of poor glycemic control in young patients with type 2 diabetes[5)~7)14)15)]. However, these reasons are not applicable to our subjects, because ethnicity and culture were very different.

Few studies have suggested that patients with a higher uric acid or creatinine level will have better glycemic control. The serum uric acid level was correlated with creatinine ($r=0.346$, $p<0.001$) and BMI ($r=0.204$, $p<0.001$) in our study. Excessive food intake may be a common feature underlying these factors. Choi et al reported that higher insulin levels are known to reduce renal exertion of uric acid, and that the strong liner and independent association was seen between fasting serum C-peptide and uric acid levels[16)]. Therefore, patients with high serum uric acid levels were considered to have high insulin resistance, and such patients might respond well to the treatment given during 6 months.

Sex and HDL-cholesterol were excluded from multivariate analysis, although they were identified by univariate analysis. It is well known that uric acid, creatinine or HDL-cholesterol level was different between male and female, and actuary these differences were seen in our study (data not shown). Therefore, we considered that sex and HDL-cholesterol were excluded as a result of adjustment by uric acid and creatinine levels.

In the present study, a high total cholesterol level was associated with poor glycemic control, which is consistent with the report of Benoit et al[5)].

It should be noted that there was no significant difference of the mean ± SD baseline HbA_{1c} between patients with good and poor glycemic control (8.9 ± 2.1 vs. 9.1 ± 1.9%, $p=0.164$). This means that baseline HbA_{1c} value dose not affect HbA_{1c} value at 6 months.

Acute insulin response, but not HOMA-IR or HOMA-β, was identified as a predictable factor of glycemic control. However, it should be noted that MTT data was not considered as true background characteristics in a strict sense, because MTT was performed an average of 13.5 days after the first visit.

The strengths of this study were as follows. 1) Baseline data on all subjects were systematically collected from an electronic medical record system. 2) Treatment was performed according to a common protocol. 3) Laboratory tests were done at a single hospital, which should minimize variations.

Our study had the following limitations. 1) It was performed at a single specialist diabetes facility, and 65% of the new patients were referred by general practitioners, so our conclusions may not be universally applicable. 2) The factors such as socio-economic status or psychological profile, which were difficult to evaluate, were excluded from the background factors. 3) This is a historical cohort study, and the factors observed during 6 months were excluded from the main analysis. Therefore, compliance with treatment, differences in treatment policy among doctors, and hospitalization were excluded from the background factors, although they might probably influence glycemic control after 6 months.

In summary, our findings may be helpful for early identification of patients who are less likely to achieve good glycemic control. Intensive manage-

ment is needed to prevent macrovascular and microvascular complications in such patients.

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初診2型糖尿病患者における血糖コントロール予測因子の同定

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電子カルテシステムのテンプレートを用いて初診2型糖尿病患者において初診時背景因子を抽出し，6ヵ月後の血糖コントロールとの関係を調べた．2003年7月から2005年3月までの間に東京女子医科大学糖尿病センターを初診し，初診時 HbA_{1c} 6.5% 以上で6ヵ月間以上継続通院した788名を対象とした．電子カルテシステムからテンプレートを用いて，問診，身体所見，生化学検査所見，内服薬を抽出し背景因子とした．初診から6ヵ月後の HbA_{1c} 6.5% 未満を血糖コントロール良好群，6.5% 以上を血糖コントロール不良群の2群に分け，ロジスティック回帰分析を用いて両群間の背景因子を比較した．その結果，初診時に薬物療法を受けていない（オッズ比 0.46, 95%CI 0.32-0.67），尿酸値が高い（オッズ比 1.25, 95%CI 1.09-1.42），総コレステロール値が低い（オッズ比 0.80, 95%CI 0.68-0.93），血清クレアチニン値が高い（オッズ比 1.07, 95%CI 1.02-1.13），患者年齢が若い（オッズ比 0.99, 95%CI 0.97-1.00），罹病期間が短い（オッズ比 0.98, 95%CI 0.95-1.00）患者で血糖コントロールが良好になりやすかった．この研究結果により良好な血糖コントロールを得られにくい患者を初診時に同定することが可能となり，糖尿病合併症発症を予防するためにはこのような背景因子を持つ患者に対して早期から厳格な治療を開始することが必要であると考えられる．